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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/987,755	11/15/2001	Charles A. Kunsch	PF198D1C1	7518

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EXAMINER	
KAPUST, RACHEL B	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/987,755	KUNSCH ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,7,9,10,14-16 and 18-45* is/are pending in the application.

4a) Of the above claim(s) *7,9,10 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 18-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (encompassing originally filed claims 1 and 3 and new claims 18-45) is acknowledged. The traversal is on the ground(s) that a search of the claims of Group I would overlap with a search of Groups II-VIII, and there would not be a serious burden imposed on the examiner.

Applicant's arguments have been fully considered and have been found to be partially persuasive. Claim 4 (the remaining claim from Group II) will be examined with the claims of Group I.

Regarding Applicant's argument that there is not a substantial search burden on the Examiner, as stated in the office action of paper no. 082603, the different groups of nucleic acids, proteins, antibodies, and methods represent different inventions and require different, non-contiguous searches, as evidenced by their different classification. They require separate searches of separate databases. A search for nucleotide sequences that encode a protein yields no comparison of that protein to other proteins; such comparison requires a separate search that yields no comparison of one polynucleotide sequence to another. The search for antibodies is additionally separate because it requires identification of antibodies that could be cross-reactive and thus inherently anticipate the claimed invention. The search for methods of use is separate because it requires additional considerations as to the methodology itself. Thus to consider all of these groups would constitute an undue burden because each requires considerations that are separate from each of the others.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection

are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

The restriction requirement is still deemed proper and is therefore made FINAL. Claims 7, 9-10, and 14-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 1, 3, 4, and 18-45 are under consideration.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

It is noted that Applicants claim priority to nonprovisional applications 09/263,625 and 08/464,600. Following the specific reference to each of the earlier filed applications, the status of the nonprovisional parent application(s) (whether patented or abandoned) should also be

included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Specification

The use of the trademarks BACULOGOLD™ and GENECLEAN™ have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 3, 4, and 18-45 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 1, 3, 4, and 18-45 are drawn to a polynucleotide encoding a hepatoma-derived growth factor (HDGF-2) and methods of expressing same. The claimed polynucleotide is not supported by either a specific and substantial asserted utility or a well-established utility.

A specific and substantial utility is one that is particular to the subject matter claimed and that identifies a "real world" use for the claimed invention. See *Brenner v. Manson*, 148 U.S.P.Q. 689 (1966):

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. . . . [u]nless and until a process is refined and developed to this point-where

specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

The specification teaches that the HDGF-2 polynucleotide was discovered in a cDNA library derived from human umbilical vein endothelial tissue, and it is structurally related to the HDGF family (p. 4). The specification further teaches that the protein encoded by the polynucleotide is 23% identical to human HDGF (p. 4). The specification also teaches that HDGF-2 DNA can be obtained from heart, brain, and skeletal muscle. However, tissue-specific expression is not specific to the claimed polynucleotide because it does not depend on any characteristics of the protein.

In addition, based on the reported and speculative properties of HDGF, the specification teaches that a protein encoded by HDGF-2 can be used for stimulating cell growth, particularly vascular endothelial cell growth, neuronal cell growth, and chondrocyte cell growth (p. 17). Although HDGF-2 may stimulate cell growth, no functions are actually known to be associated with the protein. The specification further teaches the HDGF-2 can be used therapeutically to stimulate vascularization of ischaemic tissues, to stimulate mesodermal induction and limb regeneration in early embryos, to promote healing in wounds due to injuries, burns, surgery, and ulcers, to treat and prevent neuronal damage due to neuronal disorders, and to enhance bone and periodontal regeneration (p. 17). While Applicants list a number of diseases in which the encoded protein might be involved, the specification does not disclose any diseases or conditions known to be associated with the encoded protein. Merely listing a number of possibilities is not sufficient to identify or confirm a "real world" context of use; clearly further research would be required to identify a disease in which the encoded protein is involved. Thus, further research is required to identify a disease for which it could be used, or a disease for which its presence would be diagnostic. See *Brenner v. Manson*, noting that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." A patent is therefore not a license to experiment.

The specification does not provide any factual evidence regarding the actual physical or chemical properties of the protein predicted to be encoded by HDGF-2. Furthermore, the specification does not provide any evidence that the protein encoded by HDGF-2 shares any of

the reputed biological activities of the HDGF protein known in the prior art. Absent factual evidence, a percentage similarity of 23% is not deemed to reasonably support to one skilled in the art whether the biochemical activity of the claimed subject matter would be the same as that of a known biomolecule with a similar sequence. It is known for nucleic acids as well as for proteins that even a single nucleotide or amino acid change or mutation can destroy or substantially change the function of the biomolecule. The effects of these changes are largely unpredictable as to which ones will have a significant effect on structure, folding, activity, etc. Thus, the citation of sequence similarity results in an unpredictable and therefore unreliable correspondence between the claimed proteins and HDGF and therefore lack support regarding utility.

The invention also lacks a well-established utility. A well-established utility is a specific, substantial, and creditable utility that is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material. The specification fails to assert any activity for the encoded protein other than those generally recognized to be attributes of hepatoma-derived growth factors. The only connection between the encoded protein of the invention and hepatoma-derived growth factors is that HDGF-2 is 23% identical to HDGF. However, all identified members of the HDGF family contain a well-conserved N-terminal amino acid sequence called the "hath" region (see Izumoto *et al.* (1997), *Biochem. Biophys. Res. Comm.* 238: 26-32 and Kishima *et al.* (2002), *J. Biol. Chem.* 277(12): 10315-10322). HDGF-2 of the current application does not contain a well-conserved hath region. Moreover, even if HDGF-2 were a member of the HDGF family of proteins, the specific function of HDGF is still unknown, and even though it is known that HDGF is a nuclear targeting molecule, the nuclear function of HDGF is unknown (Everett *et al.* (2001), *J. Biol. Chem.* 276(40): 37564-37568). There is therefore no well-established utility for members of this family; they are involved in many different processes and utility is specific to the individual protein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, and 18-45 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 31-45 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The invention appears to employ novel biological materials, specifically the cDNA of the clone deposited as ATCC Deposit No. 97163 on May 24, 1995. Since the biological materials are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological materials. It is noted that Applicants have deposited the biological materials (p. 4 of the specification), but there is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit has *not* been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years of 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become unviable.

Applicant's attention is directed to MPEP § 2400 in general, and specifically to § 2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include this information, however Applicants are cautioned to avoid the entry of new matter into the specification by adding any other information.

Claims 23-30 and 38-45 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, were it enabling for a polynucleotide comprising SEQ ID NO: 1 or encoding a protein comprising SEQ ID NO: 2, would still not reasonably provide enablement for a polynucleotide encoding at least 30 or 50 contiguous amino acid residues of SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, such as various sites or

regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. For example, Everett *et al.* (2001) teach that a single Lys to Asn mutation in HDGF blocks nuclear entry (p. 37564).

However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein that are tolerant to change and the nature and extent of changes that can be made in these positions. For instance, SEQ ID NO: 2 is a protein consisting of 249 amino acids, and claims 23-30 and 38-45 are drawn to polynucleotides encoding proteins comprising at least 30 or 50 contiguous amino acid residues of SEQ ID NO: 2. These proteins could have structures that are very different from that of SEQ ID NO: 2. The specification provides no guidance as to which (if any) of the amino acids can be changed or deleted to yield a functional equivalent of the HDGF-2 protein. Applicants have provided no guidance as to which amino acid residues are required for protein function. Even if an active site or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues.

Due to the large quantity of experimentation necessary to generate the infinite number of polynucleotides recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claims 23-30 and 38-45 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a

genus, *i.e* polynucleotides encoding proteins comprising at least 30 or 50 contiguous amino acid residues of SEQ ID NO: 2. Applicants have disclosed one species, the polynucleotide comprising SEQ ID NO: 1, but have not disclosed sufficient species for the broad genus of any polynucleotide encoding a protein comprising at least 30 or 50 contiguous amino acid residues of SEQ ID NO: 2.

The instant disclosure of a single species of nucleic acid does not adequately describe the scope of the claimed genus, which encompasses a substantial variety of subgenera including full-length genes. A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of polynucleotides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other HDGF molecules are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides encompassed: there is no guidance in the art as to what the defining characteristics of HDGF-2 might be. Thus, no identifying characteristics or properties of the instant polynucleotides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, the disclosure of SEQ ID NO:1 is insufficient to describe the genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Conclusion

NO CLAIMS ARE ALLOWED.

The following articles, patents, and published patent applications were found by the Examiner during the art search while not relied upon are considered pertinent to the instant application:

Strausberg R.L. *et al.* (2002), *PNAS* 99(26): 16899-16903

Strausberg R.L. *et al.*, NCBI Accession No. BC032855, Homo sapiens cytokine-like nuclear factor n-pac mRNA, with apparent retained intron, submitted June 7, 2002

New L. *et al.*, NCBI Accession No. AF326966, Homo sapiens cytokine-like nuclear factor n-pac mRNA, complete cds, submitted December 7, 2000

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (703) 305-0634. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm. Please note that as of January 20, 2004, the examiner's new telephone number will be (571) 272-0886.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (703) 308-4623. The fax phone number for the organization where this application or proceeding is assigned is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

RBK
1/12/04

JANET ANDRES
PATENT EXAMINER